Correlation of Quantitative MRI-derived Tumor Characteristics with Histology in Breast Cancer Murine Models

Anna G Sorace[1,2], Stephanie L Barnes[1,2], Jennifer G Whisenant[1,2], Mary E Loveless[1], and Thomas E Yankeelov[1,2]

[1]*Radiology and Radiological Sciences, Vanderbilt University, Nashville, Tennessee, United States,* [2]*Vanderbilt University Institute of Imaging Science, Vanderbilt University, Nashville, Tennessee, United States*

Purpose

The goal of this study is to identify the relationship between the apparent diffusion coefficient (ADC, from diffusion weighted MRI, DW-MRI), the extravascular extracellular volume fraction (v_e, dynamic contrast enhanced MRI, DCE-MRI), and histology measurements. We report DCE- and DW-MRI preclinical studies obtained from two breast cancer murine models to examine the relationship between *in vivo* measurements of ADC and v_e and the actual extracellular space (%EC) quantified by *ex vivo* histology.

Methods

Nude athymic mice were injected with either 10^7 HER2+ BT474 (n=15) or triple negative MDA-MB-231 (n=20) breast cancer cells and tumors grew to an average volume of 250 mm^3. Tumors were treated with either Herceptin (10 mg/kg), Abraxane (10 or 25 mg/kg), or saline, and animals were imaged prior to any treatment to obtain DCE- and DW-MRI data at baseline (t_0), during treatment (t_1), and on the endpoint day (t_2). Diffusion-weighted images were acquired using a standard pulsed gradient spin echo sequence with three *b* values (150, 500, and 800 s/mm^2) with the following acquisition parameters: *TR*/*TE* = 2000/30 ms, gradient duration = 3 ms, gradient interval = 20 ms, two signal excitations, 15 (1 mm) thick slices, acquisition matrix = 64 × 64, and FOV = 28 × 28 × 15 mm^3. Dynamic T_1-weighted images were acquired using a spoiled gradient echo sequence at a temporal resolution of 12.8 seconds for 20 minutes with the following parameters: *TR*/*TE* = 100/2.1 ms, α = 25°, NEX = 2, acquisition matrix = 64 × 64, FOV = 28 × 28 × 15 mm^3, and 15 (1 mm) slices. Baseline images were acquired, then a bolus of Gd-DTPA (0.05 mmol/kg) was administered. A voxel-based DCE-MRI analysis, employing the standard Tofts model and a population AIF[1], was performed to return parametric maps of v_e. After imaging acquisitions, the tissue was resected and evaluated by histological analysis. Tissue samples were embedded and sectioned so as to obtain a central slice, which was then stained using H&E. The slides were scanned using a digital brightfield microscope (20x), and thresholding techniques were utilized to segment the image based on H&E staining and calculate the percent extracellular space (%EC).

Results

For both BT474 and MDA-MB-231, the central slice median ADC exhibited a significantly positive correlation with corresponding %EC as measured by H&E (p = 0.03, p = 0.01, respectively) at t_2. Conversely, median v_e showed no correlation with %EC (p = 0.06 and p = 0.89 for BT474 and MDA-MB-231 tumors, respectively) at t_2. Additionally, there was no correlation discovered between ADC and v_e with either whole tumor analysis or central slice analysis (p > 0.05). Combination data (Figure 1) reveals a highly significant correlation between ADC and %EC (r = 0.80, p < 0.001); however, no correlations were seen between v_e and %EC, and v_e and ADC.

Discussion

The use of biomarkers available from quantitative DCE- and DW-MRI to assess tumors and their response to therapy has shown considerable potential[2,3]. However, successful application and clinical translation of these techniques demands that they be properly qualified. While ADC correlates well with the %EC, this data adds to the growing body of literature which suggests that v_e derived from DCE-MRI is not a reliable biomarker of %EC. The lack of a correlation between v_e and histology could potentially be attributed to the modeling approaches commonly used in DCE-MRI. For example, the Tofts models often return unphysiological values of v_e because the model does not account for the presence of contrast agent diffusion[4].

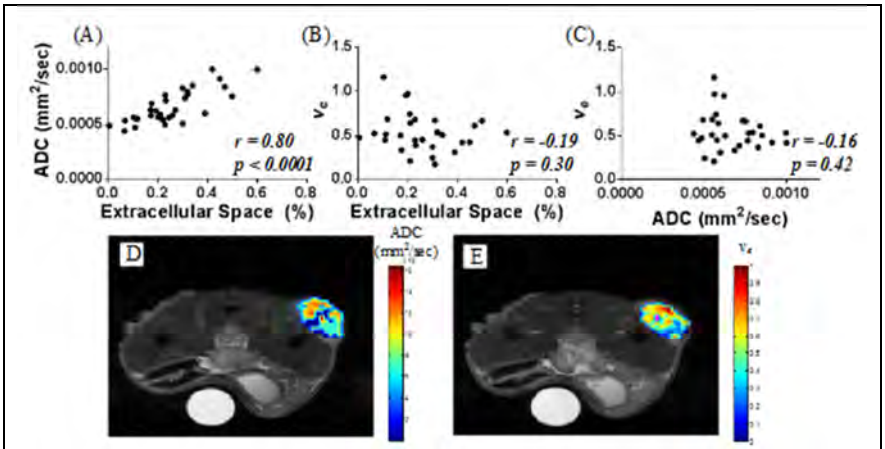

Figure 1. *Breast cancer preclinical data reveals a* ***(A)*** *positive correlation between ADC and %EC. No correlation was seen between* ***(B)*** v_e *and %EC, and* ***(C)*** v_e *and ADC. Panels D and E present representative maps of ADC and* v_e*, respectively.*

Conclusion

This data suggests that v_e is not a reliable biomarker of the extracellular extravascular space. Conversely, ADC appears to be a reliable method for noninvasively evaluating extracellular space in preclinical breast cancer models.

References

1. Loveless et al. Magn Reson Med. 2012; 67:226-36.
2. Yankeelov et al. Nat Rev Clin Oncol, 2014: 11:670-80.
3. Chung et al. J Med Imaging Radiat Oncol, 2014:5.
4. Barnes et al. PLoS One, 2014:9.

Acknowledgments

NCI R01 CA138599, NCI P50 CA098131, NCI P30 CA68485, NCI R25 CA092043, NCI 5T32 CA093240 and NCI U01 CA174706.